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Title : DANTROLENE AND TRANSMITTER MOBILIZATION

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Introduction. Dantrolene (Dantrium) is a muscle relaxant which has a direct action on skeletal muscle fibers to decrease the strength of contractility and is used clinically in cases of spasticity[1] and recently prophylactically for the control of malignant hyperthermia[2]. Previous workers[3] have reported that dantrolene has an action on the nerve terminal at the amphibian neuromuscular junction to decrease the frequency of miniature endplate potentials (MEPPs). The aim of the present study was to determine if dantrolene has a presynaptic action on spontaneous and evoked release of acetylcholine at the mammalian neuromuscular junction.

Methods. Rat phrenic nerve-hemidiaphragm preparations were pinned to the base of a small organ bath and bathed with physiological solution oxygenated with 95% O_2/5% CO_2 and maintained at 32 C. Conventional electrophysiological intracellular recording techniques were used. Control recordings of trains of 80 endplate potentials (EPPs) elicited at frequencies of nerve stimulation of 0.1, 2, 25, 50 and 100 Hz were made from endplates in physiological solution containing 2 µM (+)-tubocurarine alone and then repeated after at least 30 min of soaking in an identical solution containing 20 µM dantrolene. The number of quanta, or packets, of acetylcholine released during each EPP was estimated by the method of variance[4] using the amplitude of the last 70 EPPs of the train. The mobilization of transmitter (quanta/sec) was calculated from the EPP quantal content and frequency of nerve stimulation.

Results. No change of resting membrane potential nor mean EPP amplitude was observed during exposure to 20 µM dantrolene compared to control, however a significant reduction of the mean EPP quantal content and the mobilization rate was observed at frequencies of nerve stimulation of 50 and 100 Hz. Mean EPP quantal content was significantly ($P<0.05$) reduced from 50 ± 8 to 30 ± 7 and the mobilization rate from 2475 ± 402 to 1486 ± 336 quanta/sec at 50 Hz by exposure to 20 µM dantrolene, and similarly at 100 Hz mean EPP quantal content was significantly ($P<0.05$) reduced from 36 ± 5 to 21 ± 5 and the mobilization rate was reduced from 3640 ± 469 to 2140 ± 525 quanta/sec by dantrolene. There was no significant change of any other parameters measured at 50 and 100 Hz and also at frequencies of 25 Hz and lower no change of any of the parameters measured was observed. No significant change of MEPP frequency was observed, 2.9 ± 0.2 Hz in control compared to 3.1 ± 0.5 Hz in 20 µM dantrolene. The discrepancy between the present results on MEPP frequency and those of previous workers is most likely due to species variation since previous workers used amphibian muscle[3].

Discussion. The results of the present study show dantrolene, at a concentration of 20 µM, to have a presynaptic action on transmitter mobilization with a subsequent decrease of mean EPP quantal content during trains of nerve stimulation at 50 and 100 Hz in mammalian muscle paralysed with 2 µM (+)-tubocurarine. However, since this effect of dantrolene occurred only at frequencies of nerve stimulation of 50 and 100 Hz in the presence of (+)-tubocurarine and mean EPP amplitude was not significantly changed it is unlikely to have any significance in a normal physiological situation. However, if transmitter mobilization were previously decreased by another drug then dantrolene could possibly have an additive action in this respect. Since dantrolene is known to interfer with calcium in muscle fibers[1] and possibly also with calcium in the nerve terminal[3] the effect of the drug on acetylcholine mobilization reported in the present study may provide further insight into the role of calcium in this process.

References:

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